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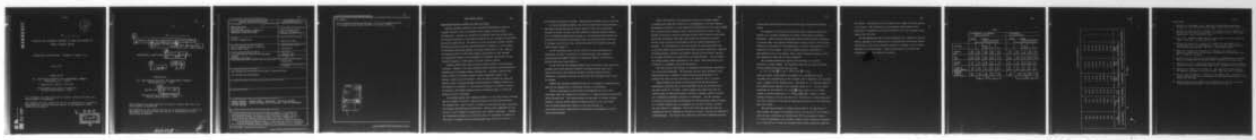

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ANNUAL PROGRESS REPORT

RESPONSIBLE INVESTIGATOR: RICHARD H. EGDAHL, M.D.

1 July 1977

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Boston University School of Medicine
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In adrenalectomized-pancreatectomized Rhesus monkeys, it was shown that hyperglucagonemia does not directly cause significant nitrogen loss in post-operative primates receiving eucaloric nutritional support and that in post-operative primates receiving reduced calories, elimination of pancreatic glucagon is associated with decreased urinary losses in nitrogen.

In adrenalectomized Rhesus monkeys, it was shown that cortisol metabolism has a defined chronologic pattern composed of the combination of a circadian

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20. Abstract

and an infradian rhythms and may play a role in the composite patterns of circadian cortisol rhythms observed in the intact animal.

ENDOCRINE AND METABOLIC RESPONSE TO SHOCK AND TRAUMA

The most prominent metabolic event observed following major trauma is a general catabolic state in association with changes in blood hormone concentrations. Patterns of utilization of metabolic fuels are altered during this period resulting in a far greater proportion of the expended calories being derived from body protein. The effects of these alterations include a general debilitation which can become life-threatening if prolonged, or if occurring in individuals previously weakened by disease, malnutrition or age. Whatever the survival benefit of this post-traumatic mobilization of body nitrogen, it is generally accepted to be detrimental if prolonged, and reversal of this catabolic response is a major goal of current clinical research.

Previous studies have related elevated glucagon levels to post-traumatic catabolism. Whether or not this catabolism results directly from inappropriate hypersecretion of glucagon remains controversial. Pozefsky's forearm study found no effect of glucagon on muscle protein catabolism; however, the systemic effect was not determined. Aoki and Cahill observed an unexpected anabolic effect of infused glucagon and hypothesized a feedback inhibition of the alpha cell to explain it. This study was designed to eliminate variables of pancreatic and adrenal hormone secretion following surgery to assess the catabolic potency of glucagon.

Forty Rhesus monkeys were randomly assigned to a low calorie group receiving D5W (24 cal/Kg/24 hr) and to a high calorie group receiving D25-4% Freamine (80 cal/Kg/24 hr). After 24 hours of infusion, total pancreatectomy, splenectomy and bilateral adrenalectomy were performed. Hydrocortisone (8mg/Kg/24 hr) and Insulin (.5 and 3 U/Kg/24 hr respectively) were infused continuously. Glucagon was continuously infused at two different doses to 2 sub-groups of animals in each group to establish serum insulin/glucagon molar ratios of 4 and 0.4. A

third subgroup received no glucagon. Splenectomized monkeys served as controls.

In the well-alimented monkeys, low I/G molar ratios (0.4) were associated with high blood FFA and glucose levels; however, there was no significant increase in urinary nitrogen loss when compared to glucagon deprived animals. Lack of exogenously administered glucagon in the pancreatectomized monkeys was associated with elevated blood alanine levels and decreased urinary excretion of nitrogen in the form of urea, alterations which were reversed by glucagon administration (table 1).

In the low-calorie group, low I/G ratios (0.4) were associated with significant increases in excretion of urinary nitrogen, when compared to glucagon deprived animals; however, no significant effects on blood FFA or glucose levels were noted (table 1).

It was concluded that hyperglucagonemia does not directly cause significant nitrogen loss in post-operative primates receiving eucaloric nutritional support and that in post-operative primates receiving reduced calories, elimination of pancreatic glucagon is associated with decreased urinary losses in nitrogen.

Whether post-operative endogenous production of glucagon is inappropriately high for the ongoing state of starvation remains to be determined.

Further investigation on the metabolic derangements that occur after hemorrhagic shock and trauma will be carried on in a Rhesus monkey model developed during the past year. This model provides an opportunity to develop combined studies of limb and hepatic metabolite balance as well as the conventional total nitrogen balances.thus assess in a more detailed way the post-traumatic protein hypercatabolism and hepatic gluconeogenesis and their regulating mechanisms.

Initial difficulties in our studies in the area of circadian rhythms of hormones and trauma were related to the establishment of the most adequate environmental conditions to avoid undesirable interference with the normal rhythms. After extensive pilot studies in which isolation booths were tried, it was decided to develop an isolation room where animals would be kept in restraining chairs with intravenous lines that would enable the collection of samples without contact between the investigators and the animals undergoing an experiment. It is interesting to note that animals in restraining chairs kept in isolation booths under controlled dark/light cycles and temperature conditions developed Cushing's syndrome with markedly elevated cortisol levels, abscence of circadian variation in cortisol levels and high mortality. In five animals the adrenal glands showed hyperplasia of the cortex. These disturbances were attributed to confinement and social deprivation.

The first protocol was designed to determine the chronologic characteristics of cortisol metabolism. The hypothesis was that since peripheral blood concentrations are a composite of both production and metabolism, it is possible that there is also a variation in the metabolic rate of cortisol.

Rhesus monkeys were placed in restraining chairs and maintained in environmental isolation with 12 hours dark/light cycles and ad libitum food and water intake for 7-15 days. Control samples were drawn every hour for 48 hours after the adaptation period to provide an adequate number of results for a meaningful mathematical analysis of rhythmicity. This was followed by bilateral adrenalectomy and replacement with hydrocortisone sodium succinate at a constant infusion rate of 6 μg/kg/min for the first 72 hours; the dose was then reduced to 3 μg/kg/min. On the 3rd or 5th post-operative days the sampling protocol was repeated for 48 hours or 24 hours. Cortisol was measured by radioimmunoassay. The results were subjected to non-linear regression analysis

fitting sine-cosine models which could reflect both circadian and infradian cycles.

The analysis of our data from the chaired intact primates confirmed the presence of a circadian rhythmicity of cortisol levèls without modifying components. After bilateral adrenalectomy and with hydrocortisone replacement at constant rates, the temporal distribution of plasma cortisol concentrations exhibited, in the majority of the experiments, a pattern characterized by the combination of two rhythms. The first component showed a periodicity of approximately 24 hours (circadian), while a second component presented cycles with durations of less than 24 hours (infradian).

The following mathematical analysis was developed for a precise definition of these rhythms. The regression model that was used to describe the post-adrenalectomy results had the form:

$$y_t = A_o + A_1 \cos\left(\frac{2\pi}{24} t + B_1\right) + C^{|t|} A_2 \cos\left(\frac{2\pi}{P} t + B_2\right)$$

where y_t=cortisol concentrations; A_o=average of y_t; A_1=amplitude of the circadian cycle; A_2=amplitude of the infradian cycle; Bl=phase of the circadian cycle; B_2=phase of the infradian cycle; P=duration of the infradian component and C=damping factor applied to the infradian rhythm ($C < 1$). The first major constituent of this function, i.e. $A_1\cos(\frac{2\pi}{24}t+B_1)$, reflects the circadian rhythm; the second constituent, i.e. $C^{|t|} A_2\cos(\frac{2\pi}{P}t+B_2)$, explains a damped infradian rhythm (a cycle of less than 24 hr. duration with a fading amplitude). The total variability of the data is significantly explained by this regression model ($p < 0.001$).

The calculated averages of cortisol concentrations, the amplitudes of both rhythms, the values of the damping factors, the duration of the infradian cycles and the coefficients of determination (R^2) are presented in Table 2. In 7 out of 8 experiments, the circadian component showed significant amplitude at $p < 0.05$ and in 6 of them the infradian rhythm showed significant amplitude

at $p < 0.05$. The duration of the infradian cycles ranged from approximately 3 to 16 hours. The coefficient of determination, which indicates the proportion of variability of the data accounted for by the regression model, ranged from 78 to 97%.

We have demonstrated that cortisol metabolism has a defined chronologic pattern composed of the combination of a circadian and an infradian rhythms and may play a role in the composite patterns of circadian cortisol rhythms observed in the intact animal. These findings must be considered when aberrations in hormone rhythms are analyzed.

TABLE 1

	25% DEXTROSE - 4% FREAMINE (80 Cal/kg/24hr)					5% DEXTROSE (24 Cal/kg/24hr)				
	PREOP	POSTOP				PREOP	POSTOP			
		Control	Pancreatectomized Adrenalectomized				Control	Pancreatectomized Adrenalectomized		
I/G RATIO	-	-	No Glucagon	4.0	0.4	-	-	No Glucagon	4.0	0.4
GLUCOSE mg%	238 ±22	264 ±52	250 ±40	206 ±39	450 ±53	122 ±17	110 ±19	121 ±56	164 ±45	180 ±53
FFA uM/cc	.521 ±.06	.471 ±.08	.406 ±.07	1.40 ±.28	1.24 ±.15	1.19 ±.06	.982 ±.26	1.02 ±.23	.998 ±.36	1.087 ±.04
ALANINE uM/cc	.59 ±.1	.35 ±.11	1.44 ±.10	.67 ±.05	.53 ±.11	.35 ±.11	.52 ±.03	1.30 ±.10	.80 ±.09	.54 ±.45
% UREA in URINE NITROGEN	88 ±4	82 ±3.5	63 ±3.1	85 ±5.7	85 ±2.7	82 ±4.2	88 ±3.4	65 ±4.1	81 ±4.2	91 ±4.1
NITROGEN BALANCE mg/kg/24hr	+51 ±34	-97 ±36	-24 ±98	-115 ±40	-101 ±79	-419 ±34	-407 ±44	-240 ±18	-298 ±25	-381 ±59
		$p > 0.25$		$p > 0.30$			$p < .0125$		$p < 0.05$	

TABLE 2

EXPERIMENT #	AVERAGE CORTISOL CONCENTRATIONS (A_o) (µg%)	AMPLITUDE OF CIRCADIAN CYCLE (A_1) (µg%)	AMPLITUDE OF INFRADIAN CYCLE (A_2) (µg%)	DAMPING FACTOR (C)	DURATION OF INFRADIAN CYCLE (P) (hours)	COEFFICIENT OF DETERMINATION (R^2)
1	102.53	25.26 *	70.76 *	0.55	7.67	96%
2	84.53	6.44 *	56.15 *	0.58	9.88	92%
3	215.79	111.45 *	158.96 *	0.93	16.08	96%
4	212.83	19.43	271.04 *	0.61	11.92	92%
5	164.39	28.49 *	58.67 *	0.37	2.93	78%
6	105.45	29.09 *	9.70	0.99	5.57	80%
7	131.80	64.26 *	13.74 *	0.99	7.97	97%
8	102.25	24.58 *	34.54 *	0.63	24.85	90%

* significant at $p < 0.05$

PUBLICATIONS

1. Whitten, R.H. and Egdahl, R.H.: High-dose glucose-insulin-potassium in treatment of irreversible hemorrhagic shock. Surg. Forum 27:60, 1976.

2. Clarke, J.R., Whitten, R.H., Williams, L.F., Hirsch, E.F. and Egdahl, R.H.: Elevated red-cell sodium concentration in patients in shock: sources and significance. Surg. Forum 27:47, 1976.

3. Ryan, N.T.: Metabolic adaptations for energy production during trauma and sepsis. Surg. Clin. N. Amer. 56:1073, 1976.

4. George, B.C., Ryan, N.T., Culver, P.J., Lowey, B.P. and Egdahl, R.H.: Contrasting effects of cycloheximide on protein turnover of human skeletal muscle versus rat diaphragm. Fed. Proc., 1977 Abstract #4806.

5. Ryan, N.T., George, B.C., Harlow, C.L., Hiebert, J.M., Egdahl, R.H.: Endocrine activation and altered muscle metabolism after hemorrhagic shock. Amer. J. Physiol. (in press)

6. Ryan, N.T. et al: Role of the adrenal glands in the metabolism of skeletal muscle from streptozotocin diabetic monkeys. (submitted for publication).

7. George, B.C., et al: Persisting structural abnormalities in liver, kidney and muscle tissues following hemorrhagic shock. (submitted for publication).

8. Egdahl, R.H., Meguid, M.D. and Aun, F.: THe importance of the endocrine and metabolic responses to shock and trauma. Crit. Care Med. (in press).

9. Aun, F., Lee, A., Mattox, S., Meguid, M. and Egdahl, R.H.: Evidence for a rhythmic variation of cortisol metabolism in adrenalectomized primates. Surg Forum, 1977 (in press).

10. Whitten, R.H., Aun, F., Meguid, M. and Egdahl, R.H: The role of glucagon in post-operative catabolism. Surg. Forum, 1977 (in press).

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